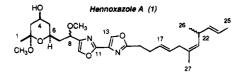
Total Synthesis of the Enantiomer of the Antiviral Marine Natural Product Hennoxazole A

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A large number of extracts from marine organisms show moderate to high activity in antiviral screening essays and might therefore prove useful as a source of unconventional lead structures in the development of effective drugs against viral diseases.¹ Hennoxazole A (1) was isolated by Ichiba et al.² from a marine sponge, a Polyfibrospongia sp. (phylum Porifera), and was shown to be highly active against herpes simplex virus (HSV-1, IC₅₀ = 0.6 μ g/mL). This structurally diverse natural



product incorporates a bisoxazole, a pyranoid glycoside, and a skipped triene unit. The relative configuration at C(2), C(4), and C(6) was determined by NMR experiments;² the absolute configuration as well as the stereochemistry at C(8) and C(22)remain unresolved.

As a part of our program for the synthesis and study of marine natural products,³ we have recently embarked on the total synthesis and structure elucidation of hennoxazole A. In this communication, we report the preparation of the (2S,4S,6S,8S,-22R)-isomer 2. Key features of our synthesis are (1) a highly convergent strategy that combines pyran and triene segments via a novel bisoxazole synthesis; (2) the use of a m-xylene as a pyran synthon; (3) a vinyl cuprate $S_N 2$ displacement of a sterically hindered allylic ester at C(22).4

For the synthesis of the left side (C(1)-C(10)) segment of hennoxazole A, an Evans-Mislow rearrangement⁵ of the S-oxide of thioether 4 provided the (E)-allylic alcohol 5^6 in >96% diastereomeric purity (Scheme 1). Sharpless asymmetric epoxidation⁷ followed by oxirane reduction with Red-Al⁸ introduced the secondary alcohol function at C(6) that was used as a linchpin for the construction of the pyran stereocenters at C(2) and C(4). Selective silvlation of the primary alcohol and dissolving metal reduction yielded the diene 6 in seven steps and 35% overall yield from commercially available mercaptoimidazole (3). Ozonolysis followed by reductive workup completed the unraveling of the β -diketone functionality from the meta-substituted xylene.⁹ After treatment of the complex mixture of keto-enol as well as cyclic isomers of the intermediate 6-hydroxy-8-silyloxy-2,4-octanedione with p-TsOH in THF,

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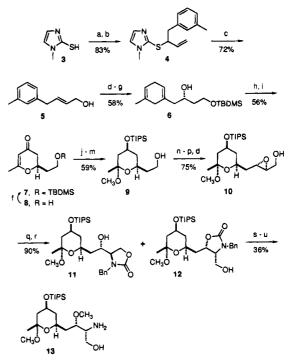
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Scheme 1^a



^a (a) Allyl bromide, 6 M NaOH, CH₂Cl₂, BnNEt₃Cl, 35 °C. (b) n-BuLi, a-bromo-m-xylene, THF, -78 °C to 20 °C. (c) MCPBA, MeOH, -30 °C to 20 °C; then Et₂NH, 20 °C. (d) tert-Butyl hydroperoxide, L-(+)-diisopropyl tartrate, Ti(O-i-Pr)4, 4 Å MS, -20 °C. (e) Red-Al, THF, -15 °C. (f) TBDMSCl, Im, CH₂Cl₂. (g) Li, NH₃, tert-amyl alcohol, THF, -40 °C. (h) O₃, EtOAc, -78 °C; then H₂, Pd(OH)₂, 20 °C. (i) TsOH, THF, 20 °C. (j) NaBH₄, CeCl₃, THF/MeOH, -20 °C. (k) TIPSCI, Im, DMAP, DMF. (l) HC(OMe)₃, MeOH, PPTs, benzene, 20 °C. (m) LiOH, dioxane/EtOH/H2O, 90 °C. (n) TPAP, NMO, 4 Å MS, CH₂Cl₂, 20 °C. (0) (EtO)₂P(O)CH₂CO₂Et, NaH, THF, 0 °C. (p) DIBALH, THF, 0 °C. (q) BnNCO, Et₃N, CH₂Cl₂, 20 °C. (r) NaH, THF, 0 °C to 20 °C. (s) NaH, MeI, Ag₂O, THF, 0 °C to 20 °C. (t) LiOH, dioxane/EtOH/H₂O, 80 °C. (u) H₂, Pd(OH)₂, MeOH, 20 °C.

56% of a 1:2 mixture of pyranones 7 and 8 was isolated. Reprotection of the primary alcohol function with TBDMS-Cl converted 8 back to the desired silvl ether 7. 1,2-Reduction of the enone with NaBH₄ in the presence of CeCl₃¹⁰ occurred exclusively via axial attack, and the resulting secondary allylic alcohol was silvlated with TIPS-Cl and the glycal function solvolyzed in MeOH in the presence of PPTs and methyl orthoformate to give the desired axial anomer in 71% overall yield from 7. Selective cleavage of the primary TBDMS ether vs the secondary TIPS ether was best accomplished under strongly basic conditions with LiOH in a ternary mixture of dioxane/ethanol/water (1:1:2).

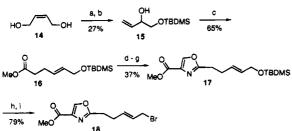
Side-chain extension of 9 to give alcohol 10 proceeded in 75% yield via oxidation with catalytic perruthenate,11 Wadsworth-Emmons reaction, DIBALH reduction, and Sharpless asymmetric epoxidation. The protocol of Kishi¹² and Roush¹³ was chosen for the introduction of the amino function at C(9). Treatment of epoxy alcohol 10 with benzyl isocyanate, followed by cyclization of the intermediate urethane, resulted in a 87:13 mixture of isomeric oxazolidinones 11 and 12. The desired major product 11 was purified by chromatography on SiO₂, O-methylated, hydrolyzed, and hydrogenated to give the amino

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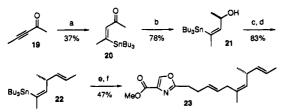
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Scheme 2^a



 a (a) HgSO4, H2SO4, H2O, 100 °C. (b) TBDMSCl, Im, CH2Cl2. (c) MeC(OMe)3, C2H5CO2H, 140 °C. (d) LiOH, MeOH/H2O, 20 °C. (e) Serine-OMe, i-BuOC(O)Cl, NEt₃, CH₂Cl₂, -15 °C to 0 °C. (f) Burgess reagent, THF, 70 °C. (g) CuBr₂, DBU, HMTA, CH₂Cl₂, 20 °C. (h) TBAF, THF, 20 °C. (i) NBS, Ph_3P , CH_2Cl_2 , -30 °C to 0 °C.

Scheme 3^a



^a (a) [(PhS)Bu₃SnCu]Li, THF, -50 °C. (b) (S)-Oxazaborolidine, catecholborane, toluene, -30 °C to -20 °C. (c) 2,4,6-Trimethylbenzoyl chloride, 2,6-lutidine, CH₂Cl₂, 20 °C. (d) [(E)-MeC=C)]₂CuLi, THF, -20 °C. (e) I₂, CH₂Cl₂, 20 °C. (f) (i) *t*-BuLi, THF, -78 °C; (ii) ZnCl₂, -78 °C to 20 °C; (iii) 18, Pd2(dba)3 °CHCl3, AsPh3, THF, 20 °C.

alcohol 13. Overall, the left-side segment was thus prepared in 21 steps and in 3% yield.

A Pd-catalyzed coupling between allylic bromide 18 and the zinc reagent derived from vinyl stannane 22 established an efficient access to the right-side (C(11)-C(25)) segment of hennoxazole A. Acid-catalyzed rearrangement¹⁴ of (Z)-butenediol (14) and silvlation of the primary alcohol function provided allylic alcohol 15 in multigram quantities (Scheme 2).

The functionalized ester 16 was readily obtained by Claisen rearrangement¹⁵ in the presence of trimethyl orthoacetate and acid. Saponification and coupling with serine methyl ester was followed by cyclodehydration with the Burgess reagent¹⁶ to give an intermediate oxazoline that was oxidized to the oxazole with cupric bromide¹⁷ in the presence of DBU and hexamethylenetetramine. O-Desilvlation and bromination¹⁸ of the allylic

alcohol led to the π -allyl palladium precursor 18. Conjugate addition of the cuprate¹⁹ derived from copper(I) thiophenoxide and Bu₃SnLi to ynone 19 provided vinyl stannane 20 in 37% yield as a single geometric isomer (Scheme 3). Asymmetric reduction of 20 with 20% tetrahydro-1-methyl-3,3diphenyl-1H,3H-pyrrolo[1,2c][1,3,2]oxazaboroleborane²⁰ in the presence of stoichiometric quantities of catecholborane²¹ gave (R)-allylic alcohol 21 in 85% ee and 78% chemical yield. After considerable experimentation, we found that conversion of 21 to the 2,4,6-trimethylbenzoate allowed a subsequent very clean S_N2 inversion with propenyl cuprate to provide the skipped diene 22 in 83% yield. Direct palladium-catalyzed coupling of the

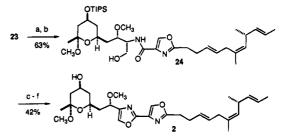
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Scheme 4^a



" (a) NaOH, MeOH/H₂O, 20 °C. (b) 13, PyBroP, EtN(*i*-Pr)₂, CH₂Cl₂, 20 °C. (c) Dess-Martin, CH₂Cl₂, 20 °C. (d) $BrCl_2CCCl_2Br$, PPh₃, 2,6-di-*tert*-butyl-4-methylpyridine, CH₂Cl₂, 0 °C to 20 °C. (e) DBU, CH₃CN, 20 °C. (f) TBAF, THF, 20 °C.

vinyl stannane with allylic bromide 18 failed due to the considerable A^{1,3}-strain in stannane 22, which was recovered unchanged from the reaction mixture. However, coupling of the corresponding vinylzinc²² reagent, which was obtained from 22 via tin iodine exchange, metal halogen exchange, and Li \rightarrow Zn transmetalation, was successful and provided the skipped triene as a single isomer. The right-side segment 23 was therefore prepared in a total of 15 steps and in 3% yield as calculated for the longest linear sequence.

The final segment condensation involved the challenging preparation of the bisoxazole moiety (Scheme 4). Coupling of the acid derived from 23 with amino alcohol 13 with the PyBroP reagent²³ provided amide **24** in 63% yield. Oxazole synthesis via oxidation/cyclodehydration²⁴ was best performed in the presence of the hindered base 2,6-di-tert-butyl-4-methylpyridine and stopped at the intermediate 10-bromooxazoline. In the presence of Et₃N,²⁴ only traces of the desired bisoxazole could be isolated. Decreased amounts of amine led to extensive cleavage of the acid-sensitive pyran portion of the molecule. The bromooxazoline was subsequently dehydrohalogenated with DBU in acetonitrile, and final desilylation with TBAF provided (2S,4S,6S,8S,22R)-hennoxazole 2 in an overall yield of 26% from the right-side segment 23.

Synthetic 2 and natural²⁵ hennoxazole A have identical highfield ¹H NMR and ¹³C NMR data. The $[\alpha]^{21}_{D}$ -47° (c 3.1, CHCl₃) for natural material is opposite to our (25,45,65,85,-22*R*)-hennoxazole 2 ($[\alpha]^{21}_{D}$ +50° (*c* 0.2, CHCl₃). In addition, CD spectra for 1 and 2 are inverted, and both compounds coelute on RP-HPLC. On the basis of these results, we propose the (2R,4R,6R,8R,22S)-stereochemistry, e.g., the enantiomer of 2, for natural hennoxazole A. Further clarification of the relative and absolute configuration of 1 will be gained by the total syntheses of additional stereoisomers, which are currently underway in our laboratories.

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Supplementary Material Available: ¹H NMR, ¹³C NMR, and HRMS spectra of 2 and ¹ H NMR spectra of synthetic intermediates; ¹H NMR spectrum of natural hennoxazole A; CD spectra and HPLC traces of $\hat{2}$ and natural hennoxazole A (28 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information. JA9430255

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